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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/565,673	08/10/90	VAN DER LAAN	J 34363/GBRD-0

EXAMINER
HENDRICKS,K

18M2/0517

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ART UNIT	PAPER NUMBER
1814	24

DATE MAILED: 05/17/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3-7-94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 4-7, 9-17, 19 & 23-26 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 4-7, 9-17, 19 & 23-26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

This Office Action is now a new non-final Action, in view of the new issues and new grounds of rejection set forth within.

The After-Final Amendment filed 9-7-93 has now been officially entered. All arguments in each of the responses has been carefully considered and are reflected herein where appropriate.

Claim 17 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 60-66,70-73 and 75-82 of copending application Serial No. 07/427,103. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant broadly-claimed "mutant high alkaline protease" encompasses the specifically claimed changes to the protease of the '103 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claim 17 is provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/427,103.

Copending application Serial No. '103 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

Claims 4-7, 9-17, 19, and 23-26 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to methods of producing an alkalophilic asporogenic Bacillus novo species PB92 of minimal indigenous extracellular protease level, transformed with a specifically-mutated B. novo PB92 alkaline protease. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The claims are not properly enabled for the recitation of a "mutant high alkaline protease", and specifically, claim 17 is further not enabled for such proteases "differing in at least one amino acid from a wild-type high alkaline protease". Applicants' arguments filed in all responses have been considered but are not deemed persuasive. Applicants have stated that "it would be well within the skill of one of ordinary skill in the

art to determine which mutations would result in a protease differing by at least one amino acid from the indigenous protease". This is not deemed persuasive, as again, one skilled in the art would not be able to determine what type of mutation, how many, at what amino acid (nucleotide on the gene), etc., including all of the millions of variations possible in order to fulfill what the applicants regard as the invention. More importantly, one skilled in the art could not prophetically predict the outcome of any mutation upon the gene, the enzyme produced, and their resultant effect upon the instantly claimed invention. This would require undue experimentation, primarily due to the unpredictable nature of the art, and the scarcity of guidance and/or working examples in the specification.

To continue, applicants have stated, at page 5-7 of the response filed 9-7-93, that "a knowledge of protease gene structure before or after mutagenesis and the effect of gene mutation on protease activity is not essential to practice the instant invention" (pg. 7). This is not deemed persuasive, as, due to the unpredictable nature of the art, supported by applicants urging of blindly producing any mutation in the protease gene, any unknown and random mutation could and would be expected to have a deleterious effect upon the protease itself, or the Bacillus organism hosting such. Improper tertiary folding, steric hinderance, or a negative effect upon the active site are just a few of the probable possibilities that would be

expected to occur to the gene itself. In addition, there is no safe predictability of what effect the mutated protease would have upon the host cell itself, or even if the gene would be translated at all.

The claims are not properly enabled for the recitation of any "mutant high alkaline protease", and any "alkalophilic Bacillus strain". Applicants have stated that the strain PB92 has been used merely as an example, and that the specification provides enablement for the use of other types of these strains, and for other "mutant high alkaline proteases". Applicants further state that techniques for such are "routine and require no inventive skill or undue experimentation" (pg. 7, response of 9-7-93). This is not deemed persuasive for the reasons of record. Primarily, the specification has not provided pertinent information regarding any other "high alkaline protease" gene, nor any appropriate Bacillus strain that would satisfy the requirements of the invention. This fact is important, as the claims are not commensurate in scope with the specification and its enablement. This information is essential to the function of the claimed invention, and the essential material may not be improperly incorporated into the specification, and does not find support within the teachings of the specification. Thus, one skilled in the art would in no way be enabled to practice the claimed invention with any such gene or strain other than the enabled Bacillus PB92.

The specification is not properly enabled for claims to any "derivative thereof" of a Bacillus novo species PB92. This phrase encompasses predetermined and random mutants of the strain, and progeny of the strain that may or may not contain the gene for the "mutant high alkaline protease" and/or a revertant strain with the indigenous gene. The specification does not properly teach nor describe to one skilled in the art these "derivatives", nor how to obtain and/or use such. Thus, this results in undue experimentation for one skilled in the art to attempt to produce such without proper guidance from the specification.

The method of claim 12 is not properly enabled by the specification. The claimed invention is not reflective of the method and "conditions whereby the replication function encoded by said vector is inactivated". It would require an inordinate amount of experimentation for one of ordinary skill to attempt to determine what and where the "replication function" of the vector is, its relationship to the rest of the invention, a method of "inactivating" such, and its possible effects upon the instant invention. Further, the specification is not enabling for any or all possible methods of "identifying" transformants with no detectable indigenous protease. The claims are not commensurate in scope with the enablement of the specification for such methods.

Claims 12, 15-16, 19 and 24-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12, third section (paragraph), recites "whereby the replication function..." (is inactivated). It is not previously described within the claim what the "replication function" is, or that it is even present in the instantly claimed invention.

Claim 15, line 2, the term "said" is incorrectly spelled as "aid". Further, the claim recites said "mutant" Bacillus strain of independent claim 14, yet claim 14 does not claim a "mutant" strain. The term "mutant" does not properly and definitely describe the transformed strain of claim 14.

Claim 16 recites deletion of the gene of claim 15 (ultimately dependent upon claim 12) "by homologous or illegitimate recombination". The independent claim 12 only recites the method by "homologous recombination", and thus claim 16 is indefinite in its improper limitation.

Claims 19 and 24-25 are indefinite in the recitation of the phrase "one or more" of the protease produced. Since only one (type of) protease is being produced in the independent claims, the claims are indefinite for the recitation of "one or more" (it is assumed that applicants do not intend for a single molecule of the protease to be "one").

The method of claim 26 is indefinite, as it is a method for producing a protease by culturing the host strain, yet there is no "recovery step" involved for obtaining the protease from the host. This is a necessary step to the claimed invention, as the mere production of the protease in the strain can not result in the claimed protease being accessible.

The amendment filed 9-7-93 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

[a protease] "exhibiting altered protease activity".

This phraseology is not supported at page 29 or anywhere else in the specification. Page 29, at best, describes "altered" protease levels of production, but does not describe the proteases having different activity. Note that the use of a "mutant protease" does not necessarily result in one "exhibiting altered protease activity".

Applicant is required to cancel the new matter in the response to this Office action.

Claims 9,14,19 and 23-26 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 4-7, 9-17, 19, and 23-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Fahnestock et al. and Estell et al., in view of TeNijenhuis and Suggs et al. The references and rejection are herein incorporated as cited in a previous Office Action.

Applicants' arguments filed in response to this rejection have been fully considered but they are not deemed to be persuasive. Applicants have state that Fahnestock et al. and Estell et al. would not lead one to the instant invention in light of the secondary references.

Initially, applicants have stated that "asporogenous Bacilli are surprisingly useful in obtaining high level expression of a mutant protease gene" (paper of 9-7-93, pg. 8). This has been considered, however, is not deemed persuasive, as this is not

properly reflected in the claimed invention. Very few of the claims recite an "asporogenic" Bacillus strain, let alone do any reflect the "unexpected" properties purported by applicants. Furthermore, the PB92 alkaline protease from the original strain of Bacillus PB92 was "produced in surprisingly high yields", according to TeNijenhuis et al. (Re. 30,602, of record), column 1, line 50. Thus, the use of the same indigenous natural promoter system and overall production system of that of the Bacillus PB92 strain would have naturally been expected to produce a "high yield" of protease.

Applicants assert that the prior art differs, as for example, since Fahnestock et al. inserts a CAT fragment to inactivate the protease sequence, there is the possibility of reversion. Applicants have stated that because of this and the fact that Estell et al. merely uses chemical mutagenesis to partially delete the native gene, that the method claims and those to the strain would not have been obvious. This is not found persuasive for the reasons of record. Fahnestock et al. does indeed use homologous recombination to delete the original functional gene, as do applicants. The fact that Fahnestock et al. replaces that with an inactive (mutant) analogous gene is not evidence of unobviousness. On the contrary, applicants have performed a similar step in the instantly claimed methods and strains. Applicants have deleted the original gene (same as Fahnestock et al.), and have replaced it with a (non-specified)

analogous "mutant" protease gene, similar to that of the reference.

The fact that Fahnestock et al. still produces extracellular proteases is not pertinent to the instant invention. Applicants themselves have not produced strains that do not produce any extracellular proteases, and thus do not differentiate from the prior art. Estell et al. only compliments this by a similar deletion, with the replaced flanking regions containing only a small portion of the original coding region of the protease. It would have been obvious to further delete the rest of the coding region, for the mere assurance of complete success of no protease activity. Estell et al. have shown that this method produces no (neutral) protease activity, and applicants method does not differ patentably from this by deleting the rest of the coding region. The deletion of entire genes from a genome is well-known and characterized, and is almost as old as genetic engineering itself. Applicants' contention that the deletion of an entire gene is an inventive concept is not deemed persuasive. Furthermore, at page 8 of the amendment filed 9-7-93, applicants themselves have stated that "the genetic technique of homologous recombination is well known in the art and is not a unique contribution of the Fahnestock et al. patent." Applicants have not demonstrated any results that would have been unexpected, unobvious, or superior to that taught by the prior art, absent convincing evidence to the contrary.

Again, the limitation of "an alkalophilic Bacillus strain" does not render the claim patentably distinct from the similar methods of Fahnestock et al. and Estell et al., per se. The systems are the same, and both used with Bacillus organisms, of which many are already alkalophilic. Further, the mutation of the strain to produce an "asporogenic" variant is obvious and well known in the art to do, and is easily obtained via classic UV mutation techniques, also described in Fahnestock et al. The fact that Estell et al. state that asporogenic Bacilli are "unsatisfactory" for production of heterologous proteins is not persuasive or particularly pertinent, as Fahnestock et al. preferably teach both how to make and use asporogenic Bacilli to produce heterologous proteins. Thus, the method and Bacillus strain claims are not deemed patentable in view of the prior art.

Regarding the claims (17,19 and 24-25) directed to the protease itself, methods of making detergent compositions and using laundry processes containing such, these would have been obvious extensions of the rejected claims above as well. The protease of claim 17 does not initially appear to appreciably and patentably differ from the natural protease described by TeNijenhuis, wherein natural mutations of "at least one amino acid" would be expected to occur. Further, the simple production of the protease from the method/strain claims rendered obvious above would not have involved an inventive step, and would have been obvious from the methods themselves. Also, TeNijenhuis

describe washing and detergent compositions and methods of cleaning/laundry processes using the high alkaline protease of strain PB92. Thus, the incorporation of the claimed protease into such compositions and methods would have been obvious given the teachings of TeNijenhuis.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Hendricks whose telephone number is (703) 308-2959.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180

KDH
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May 16, 1994